CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020007/S022

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

Supplemental NDA:	20-007/S-022 MAR 12 1997
Date Submitted:	May 6, 1996
Sponsor:	Glaxo Wellcome Inc.
Drug:	ZOFRAN® [ondansetron (=OND) hydrochloride] INTRAMUSCULAR INJECTION
Pharmacological Category:	Antiemetic. Selective, competitive antagonist at the 5-hydroxytryptamine receptor type 3 ($5\text{-}HT_3$)
Proposed Indication:	Single 4 mg intramuscular dose injection as an alternative to intravenous administration in the prevention of postoperative nausea and vomiting.
Material Submitted:	Three study reports 1. Report UCP/95/056 Comparison of the efficacy of 4 mg OND I.M. vs 4 mg OND I.V. in the Ipecacuanha model of emesis in healthy volunteers 2. Report GPK/91/025 PKs and Tolerability of OND 4 mg given as an I.M. injection 3. Report WMH/91/017 A pilot study to determine the tolerability and PKs of I.M. OND 4 mg
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

I. BACKGROUND/RATIONALE

Ondansetron (ZOFRAN®) is a selective $5\text{-}HT_3$ receptor antagonist. An intravenous dosage form of OND (4 mg) has been approved for the prevention of postoperative nausea and/or vomiting (PONV). For patients who have nausea and/or vomiting postoperatively, Zofran® injection (4 mg) may be given to prevent further emetic episodes (if the patient experiences nausea and/or vomiting occurring shortly after surgery). The efficacy and safety of i.v. administered OND for these indications was established with Supplement S-005 to NDA 20-007, which was approved on August, 1993.

Through the present supplemental NDA, the sponsor provides data to support the intramuscular administration of the currently approved formulation of Zofran injection as an alternative to intravenous administration in the prevention of PONV. Among the reasons listed by the sponsor in support of the I.M. route of

administration of Zofran are: 1) administration of OND would be desirable in patients experiencing ongoing emesis postoperatively when venous access is difficult to obtain or has been discontinued; 2) interruption of other medications being administered via an existing intravenous line can be avoided by I.M. administration of this or any other antiemetic and 3) emesis upon ambulation, following discontinuation of venous access, can occur in postoperative patients awaiting discharge from an outpatient surgical unit. The ability to manage emesis with I.M. administration of Zofran Injection would be important in these same day surgery patients.

In support of their request, the sponsor provided data from three clinical pharmacology studies, all of which included PK evaluations. In addition, the first study (Clinical Report UCP/95/056) included PD data. This consisted of a comparison of the efficacy of 4 mg OND given I.M. vs 4 mg of the drug given I.V. in the Ipecacuanha (**IPECAC**) model of emesis. PK results from the three studies are being evaluated by the Biopharm. Division. The present review assesses the validity of the IPECAC model. This model was used to draw conclusions on the comparative efficacy of the I.M. vs the I.V. formulation. Results of PK analyses from the three studies are only briefly reviewed here. Some emphasis is put on safety data.

II. SUMMARY OF STUDIES SUBMITTED IN NDA 20-007/S-022

As shown in Table 1, studies GPK/91/025 and WMH/91/017 were designed to compare the PKs and tolerability of OND administered as a single 4 mg I.M. dose to the same dose administered by I.V. injection. The results of these two trials demonstrated that systemic exposure to OND following I.M. and I.V. administration is equivalent based on equivalent mean AUC values. The I.M. injections were shown to be safe and well tolerated in these and other clinical pharmacology studies. The PD study UCP/95/056 compared the efficacy of Zofran injection administered intramuscularly and intravenously in the IPECAC-induced model of nausea. Results from this study are reviewed in some details in section III, below. Using this model, intramuscularly administered OND was shown to be dynamically equivalent to intravenous OND for the prevention of N&V (see Section III).

It is to be noted, however, that neither study GPK/91/025 nor (especially) WMH/91/017 established formal bioequivalence between the I.V. and I.M. routes. This is because peak serum concentration following I.M. dosing was only < half or < one-third of that following the same dose given as a 5-min. I.V. infusion. Because of the need to establish bioequivalence on PK parameters, study UCP/95/056 was carried out.

TABLE 1
NDA 20-007/S-022

Identification, Main Features of Design and Comparison of Results of PK Evaluation in Studies Submitted in Support of the Approval of Zofran® Intramuscular Injection

In all studies single 4 mg doses given either intravenously (I.V.) or intramuscularly (I.M.) were tested.

			AUC [ng-h/mL]	C_{max} [ng/mL]	t_{max} [min.]	λ [1/h]	Half-life (h)	F	REMARKS
J. Gareau UCP/95/056 (517/440) (n=56) years of age	Randomized, double blind, double-dummy, two-way, placebo-controlled crossover study with six-day washout period Single Dose; 4 mg	I.V. [n=28]	167	53.4	10.2	0.176	4.5		• Following administration of 4 mg OND, C_{max} concentrations were slightly lower and the time to t_{max} occurred later after I.M. than I.V. route. • No difference between the two routes in overall extent of absorption (based on AUC). • Both treatments were well tolerated.
		I.M. [n=28]	176	35.8	41.4	0.181	5.1	103	
P.N. Dewland GPK/91/025 (W91-016) (n=43) years of age	Randomized, double-blind, double-dummy, two-way, placebo-controlled crossover study with six-day washout period Single Dose: 4 mg	I.V. [n=16]	83.6	75.5	6.0	0.239	3.1		• I.M. ondansetron, 4 mg, produced equivalent systemic exposure (based on AUC) as the same dose of OND administered intravenously. • Peak serum concentration following I.M. dosing was < half of that following I.V. infusion • Txs were well tolerated.
		I.M. [n=17]	83.9	30.3	14.6	0.228	3.3	101	
N. Frazer L. Felgte WMH/91/017 (n=12) years of age	Randomized, double-blind, double-dummy, two-way, placebo-controlled crossover study with six-day washout period Single Dose: 4 mg	I.V. [n=6]	86.7	77.3	4.8	Not Calculated[b]			• OND 4 mg I.M. was rapidly absorbed with peak plasma concentrations averaging 23.1 ng/mL, occurring within 10 min. of administration. • Peak serum concentration following I.M. dosing was less than a third of that following the same dose given as a 5-min I.V. infusion. • Absolute bioavailability could not be assessed due to lack of data beyond 8h.
		I.M. [n=6]	78.5	23.1	8.3	Not Calculated[c]		92	

a) Composite table, assembled by M.O. from sponsor's Tables 1 and 2 (Summary). Displayed are mean data; % CV, minimum and maximum values have been omitted for clarity of presentation purposes.
b,c) Elimination rate constant and half-life were not calculated in this pilot study because sampling was only through 8h post-dose.

Also provided with this application were the results of two nonclinical irritancy studies performed in rabbits. The conclusion drawn from these two local tolerance studies was that intramuscular administration at a dose of 4 mg would be acceptable.

III. CLINICAL REPORT UCP/95/056 (Protocol 517/440)

[NOTE: The MO Review deals primarily with the "clinical efficacy" results and the validity of using IPECAC as a PD tool. Only a brief reference to the PK data is made.]

A. Objective, Design, Execution, Parameters Evaluated

This study was set to examine the relative efficacy of the I.M. vs the I.V. route of administration of OND in the prevention of emesis following a single 30 mL dose of IPECAC in 28 adult M and 28 adult F, respectively, healthy volunteers. Subjects between ages of were enrolled in four separate groups of 14 subjects each. The design of this single center study was that of a randomized, double-dummy, double-blind, 2-arm, parallel group, active-active group, gender-balanced trial.

All enrolled subjects completed the trial. Nausea assessments were to be analyzed only in the event of emetic episodes. The secondary objective was to calculate PK parameters for I.M. (test medication B) and I.V. (test medication A) OND following administration of 4 mg doses of the drug. Administration of each of the two test medications was followed 30 min. later by the administration of 30 mL of syrup of IPECAC[1], immediately followed by 200 mL water. The study population was adequate for this type of study. Material specifications, labeling, drug accountability, screening, methods of treatment assignment, blinding, concurrent therapy and proposed handling of withdrawals were all adequate.

The PDs of I.M. and I.V. OND were assessed by recording the number of emetic episodes experienced by each subject and the time to onset of emesis for a period of 11.5h after dosing with IPECAC. Additionally, nausea score assessments were made prior to administration of IPECAC and every 15 min. for 4h afterwards. This included a subjective assessment of the volunteer's worst nausea score over the previous 15 min. period. Nausea scores were rated on a 0 to 3 scale, where 0 was no nausea and 3 was severe nausea. The PKs of OND after administration of each treatment were assessed by measuring concentrations over the 12h post-dose period. Serum concentration values for OND were used for estimation of AUC_{-}, C_{max}, t_{max}, $t_{½}$ and λ_z. Matters related to QC and the handling of AEs were also adequate.

B. Study Results

1. PD Data

- There was only one incidence of emesis. This occurred in the I.V. group, ca. 4.5h after dosing with IPECAC.

[1] This supply was obtained by Glaxo Wellcome Inc. from a commercial source: 70 x 30 mL vials containing PMS-Ipecac (ipecacuanha USP, Pharmascience syrup), Lot No. 5507831, expiration date November 1996.

- Nausea data are summarized in Table 2. There was no statistically significant difference between I.M. and I.V. OND in either peak or mean nausea scores.

TABLE 2

Clinical Report UCP/95/056

ANALYSIS OF NAUSEA SCORES

	Peak Score Frequencies (n) 0	1	2	3	Total n	Weighted Mean ± SD
I.V.	18	9	0	1	28	0.065±0.126
I.M.	23	2	2	1	28	0.092±0.314
p values I.V. vs I.M.	N.S.[a]					N.S.[b] N.S.[c]

a) p-value (0.577) is based on the linear regression with integer mean score response. Independent variable is TREATMENT.
b) p-value (0.677) is based on a two-sample test.
c) p-value (0.239) is based on Wilcoxon rank-sum test. Residuals from the two-sample t-test were not normally distributed, and so treatments were compared using the Wilcoxon rank-sum test.

2. **PK Data**

Results of PK parameters for OND 4 mg administered either by the intramuscular or the intravenous route are displayed in Table 3. The I.M. route of administration was accompanied by a C_{max} that was 25% lower (32 vs 43 ng/mL; p=0.054) and a delayed t_{max} (0.38h vs 0.08h; p<0.01) an comparison to the intravenous route. These findings are not unexpected with the I.M. route of administration. On the other hand, these PK data show that I.M. OND is rapidly and completely absorbed systemically, and has an equivalent extent of absorption, as measured by AUC (161 vs 156 ng*h/mL), to I.V. OND. These AUC results were consistent with previous data. In this study, the ratio of geometric least squares means for B vs A and associated 90% confidence intervals for the log-transformed AUC and C_{max} parameters were 103% and 74% respectively. The median difference in the time to C_{max} between the I.M. and I.V. treatments was 10.2 min. The elimination rate constants (0.161 vs 0.166) were nearly identical for both routes of administration. Since there was no evidence of a difference in overall systemic absorption, and no reduction in efficacy was noted with the I.M. formulation (see PD Data above), the kinetic differences for the T_{max} and even less for the C_{max} parameters, are not considered clinically important.

TABLE 3
Clinical Report UCP/95/056

Results of Analysis of PK Parameters

	Treatment A 4 mg I.V. OND	Treatment B 4 mg I.M. OND	B/A
AUC$_\infty$ (ng*h/mL) Geometric LS Mean 95% CI Geometric LS Mean Ratio 90% CI p-value	156 (136, 180)	161 (137, 190)	103% (89%, 120%) N.S.
C_{max} (ng/mL) Geometric LS Mean 95% CI Geometric LS Mean Ratio 80% CI p-value	42.9 (33.8, 54.4)	31.9 (26.3, 38.6)	74% (58%, 96%) N.S.
t_{max} (h) Median Range Difference (A-B) 90% CI p-value	0.08 (0.08, 1.00)	0.38 (0.17, 4.00)	0.17 (0.09, 0.33) <0.001
$t_{\frac{1}{2}}$ (h) Geometric LS Mean 95% CI Geometric LS Mean Ratio 90% CI p-value	4.2 (3.6, 4.8)	4.3 (3.5, 5.3)	103% (85%, 125%) N.S.
λ_z (1/h) Geometric LS Mean 95% CI Geometric LS Mean Ratio 90% CI p-value	0.166 (0.145, 0.191)	0.161 (0.131, 0.198)	97% (80%, 118%) N.S.

CI = confidence interval
LS mean = least/squares mean

[NOTE: Summary statistics (mean, 95% CI, etc.) in this Table from the individual Clinical Report was not presented in the same manner as in the Overall Summary data (Table 1)]

3. Results of Safety Evaluations

Ondansetron, 4 mg, administered either by the I.M. or I.V. route was well tolerated. The most commonly noted drug-related AEs were diarrhea and hypnagogic effects. Establishing a causal relationship to either OND or IPECAC is difficult, although these AEs have not been commonly reported for OND; both have been noted with IPECAC administration.[2]

[2] In a study by P.A. Czajka et al. [Pediatrics. 75:1101-1104 (1985)] the incidence of diarrhea (13%) and atypical lethargy (11.6%) were significantly higher after IPECAC-induced emesis than in patients not receiving IPECAC syrup.

C. Sponsor's Conclusions

"Intramuscular and intravenous ondansetron were demonstrated to be dynamically equivalent in the prevention of emesis and nausea, using the ipecacuanha model of emesis, with respect to a one-sided equivalence criteria of 15%.

"There was no evidence of a significant difference between intramuscular and intravenous ondansetron in either peak or weighted mean nausea scores.

"C_{max} concentrations were slightly lower and the time to t_{max} occurred later after intramuscular administration than intravenous administration.

"The overall extent of absorption, as measured by AUC, showed no evidence of a difference between the two routes.

"Both treatments were well tolerated."

D. Reviewer's Comments

This trial used the IPECAC-induced emesis as a model for testing antiemetic drug activity of 5-HT_3-receptor antagonists in humans. Before assessing if this model is clinically relevant, brief comments on the PK data are made. Intramuscularly administered OND is rapidly and completely absorbed systematically and based on AUC data, has an equivalent extent of absorption to the same dose administered intravenously. The half-life ($t_{½}$) and the elimination rate constants (λ_z) were very similar with both routes of administration. Differences were shown in C_{max} concentrations (which were 25% lower with the I.M. route of administration) and in the time to t_{max} (which occurred significantly later after I.M. administration) but these findings are not unexpected with the I.M. route of administration. Since, using prevention of emesis as the parameter of evaluation, I.M. and I.V. OND were dynamically equivalent and there was no significant difference between the two routes of administration in either peak or weighted mean nausea scores, the observed kinetic differences appear to be clinically unimportant.

Clinical Relevance of the IPECAC Model

In this model, both objective parameters (vomiting) and subjective responses (nausea) were evaluated. These signs/symptoms are also observed in some patients undergoing surgical operations (specially abdominal/gynecological) under general anesthesia. PONV is influenced by many factors, including premedication, anesthetic techniques, patient predisposition, type of operation and factors related to the post-operative period. The mechanism resulting in PONV is not understood but since compounds such as OND that antagonize the 5-HT_3 receptor are effective in preventing/treating PONV, PONV must, in some way be associated with these receptors. The vomiting response is coordinated and controlled by the "vomiting center", located in the lateral

reticular formation of the brain. This center receives inputs from the gastrointestinal tract, liver, pharynx, cerebral cortex and the chemoreceptor trigger zone (CTZ) for emesis. The CTZ is located in the area postrema and monitors the level of toxins in the cerebro-spinal fluid and circulation. The main pathway from the gut to the CNS is via the vagus nerve, which relays information to the nucleus of the tractus solitarius located within the vomiting center [A.J. Freeman and M.H. Cullen, J. Clin. Pharm. Therap. 16:411-421 (1991)]. A number of studies have demonstrated that 5-HT_3 receptor antagonists are effective in the prevention/treatment of cancer chemotherapy-induced N&V. From animal work, it appears that these therapeutic agents initiate vomiting at different sites and that a single cytotoxic drug can trigger emesis simultaneous at more than one of the above-mentioned areas known to be able to induce emesis. Chemotherapeutic drugs are usually administered by intravenous infusion. These agents, or their metabolites, may be detected by the CTZ and/or may release 5-HT from the gastrointestinal tract mucosa which may depolarize vagal nerve afferents.[3] In addition to serotonin receptors, acetylcholine, dopamine, histamine, noradrenaline and adrenaline receptors are involved in the emetic reflex [P.L.R. Andrews et al., Trends in Pharmaceut. Sci. 9:334-341 (1988)]. The importance of any one type of receptor differs according to the etiology of emesis. The importance of the 5-HT_3 receptor in the etiology of emesis is further emphasized by the demonstration that the 5-HT_3 receptor antagonist OND is also effective in the prevention of radiation-induced emesis (in addition to CCNV).

IPECAC syrup is widely recommended as a household and hospital first-aid measure for accidental poisoning When the drug is given orally (30 mL on a full stomach or with water), it takes 15 to 30 min. to produce emesis. Although originally advocated only in children, IPECAC seems to be equally effective in adults [F. Kenneth et al., Med. J. Austr. 2:91-93 (1977)] and, when correctly used, may be preferable to gastric lavage. IPECAC contains a number of different alkaloids, but the emetic action of the crude drug is almost entirely attributable to the alkaloids emetine and cephaline.[4] According to Goodman & Gillman's, the Pharmacological Basis of Therapeutics, Ninth Edition [p. 71-72 (1996)], IPECAC acts as an emetic because of its local irritant effect on the enteric tract and its effect on the CTZ.

The following lines of evidence are presented in support of the thesis that 5-hydroxytryptamine plays a crucial role in the emesis induced by IPECAC and that N&V induced by IPECAC is mediated, at least in part, through 5-HT_3 receptors.

- In a study by B. Costall et al [Neuropharmacol. 29:453-462 (1990)], orally administered IPECAC (0.3 to 2.4 mg/Kg) was shown to induce emesis

[3] Indeed, pre-treating ferrets with chlorophenylalanine, an inhibitor of serotonin synthesis, prevents cisplatin-induced emesis [N.M. Barnes et al., Br. J. Pharmacol. 92(Suppl.)649P (1997)] and a significant increase in the level of the 5-HT metabolite, 5-hydroxy-indoleacetic acid has been detected in the urine of patients within 6h of cisplatin treatment [L.X. Cubeddu et al., NEJM 322:810-816 (1990)].

[4] [I.M. Rollo in: The Pharmacological Basis of Therapeutics, edited by L.S. Goodman and A. Gilman, Macmillan Publishing C9o., New York, p. 1074 (1976)].

in the ferret that was antagonized by small doses (0.1 mg/Kg i.p.) of the 5-HT_3 receptor antagonist ICS 205-930. These data indicate that IPECAC may mediate its effects through a 5-HT system.

- A randomized, double-blind, two-way crossover study was conducted in 20 HMV, aged 18 to 31 years [N.A. Minton et al., Br. J. Clin. Pharmacol. 33:221 P-222P (1992)]. The subjects received a 5-min. infusion of OND 8 mg or PL, 30 min. before oral IPECAC 30 ml. Emetic episodes were counted and nausea was assessed by VAS over an 8h period. Following PL infusion, IPECAC resulted in emesis in 19/20 subjects and nausea in the remaining subject.[5] Pre-treatment with OND prevented IPECAC-induced vomiting in all subjects and reduced nausea (maximum VAS score median score 1.4/100).

- In an additional publication, N.A. Minton et al. [Clin. Pharmacol. Ther. 54:53-57 (1993)] expanded their original observations. In a double-blind, randomized, parallel-group study, five groups of 10 healthy men received single 5-min. infusions of 8 mg, 4 mg, 1 mg, 0.25 mg or 0.1 mg OND (as hydrochloride dihydrate) 30 min. before oral administration of 30 ml syrup of IPECAC. Emetic episodes and nausea (100 men visual analog scale) were assessed over an 8-h period. There were no emetic episodes after 8 or 4 mg OND. Seven, nine and 10 subjects vomited after 1 mg, 0.25 mg and 0.1 mg OND, respectively, with median times to onset of 62, 31 and 37 min. Median peak nausea scores were 0 mm for both 8 and 4 mg OND and 30, 53 and 26 mm for 1, 0.25 and 0.1 mg OND. AEs were mild.

The authors of this publication commented that the lowest recommended single i.v. dose of OND in chemotherapy-induced emesis is 8 mg. It therefore appeared that the anti-emetic potency of OND assessed in the IPECAC model correlates better with clinical efficacy in PONV than with chemotherapy-induced emesis. A plausible explanation is that some chemotherapy regimens (i.e. high-dose cisplatin) are more potent emetic stimuli than syrup of IPECAC.

In conclusion then, IPECAC-induced emesis is a safe and representative model for testing the antiemetic potential of 5-HT_3-receptor antagonists.

Reviewer's Conclusion

Results in study UCP/95/056 demonstrate that intramuscular and intravenous ondansetron, 4 mg, are dynamically equivalent in the prevention of vomiting and nausea, with respect to a one-sided equivalence criteria of 15% in the IPECAC model of emesis. In this model, >90% of the subjects are expected to vomit within 30 min.[6] but none of the subjects receiving 4 mg intramuscular

[5] Time to onset of emesis was 14 to 121 min (median 33 min), the number of emetic episodes ranged from 0 to 6 (median 3) and the duration of emesis was 0 to 237 min (median 49.5 min). Maximum VAS score ranged from 7 to 96/100 (median max score 32.6/100).

[6] [Anonymous. Br. Med. J. 75:1101-1104 (1985); H.C. Mofenson and T.R. Caraccio, Pediatrics, 77:551-552 (1986)].

OND experienced vomit. Also, there was no significant difference between the two routes of administration in either peak or weighted mean nausea scores.

IV. RECOMMENDATIONS FOR REGULATORY ACTION

Using a relevant human PD model to assess the antiemetic effects of 5-HT_3-receptor antagonists, data have been presented that 4 mg intramuscular injection of Zofran® is as efficacious as 4 mg of intravenously administered drug, in the prevention of N&V induced by 30 mL IPECAC.

Approval of the 4 mg Zofran dose to be administered intramuscularly as an alternative to intravenous administration of the drug, at the same dose, in PONV is recommended.

March 11, 1997

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/S/
Hugo E. Gallo-Torres, M.D., Ph.D.

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NDA 20-007/S-022
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HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
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